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(19)(CA) APPLICATION FOR CANADIAN PATENT (12)

(54) Microcapsule Composition and Process

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ABSTRACT OF THE DISCLOSURE

A taste-masked free-flowing powder includes microcapsules having a particle size of approximately 300 µm or less. Each microcapsule includes an effective amount of a core element including at least one pharmaceutically active ingredient. A substantially smooth and continuous microcapsule coating on the core element is formed from a coating composition including a water insoluble polymer. The coated microcapsules exhibit a reduced dissolution profile.

MICROCAPSULE COMPOSITION AND PROCESS

The present invention relates to a microcapsule composition preferably a pharmaceutical microcapsule composition having improved coating characteristics and to a method of preparing the same.

As is known in the prior art, it is desirable in the treatment of a number of diseases, both therapeutically and prophylactically to provide the active pharmaceutical ingredient in a coated form. The coat may provide the active pharmaceutical ingredient with for example a sustained release profile, a pH dependent release profile, may function as an enteric coat, or may impart taste masked properties.

Furthermore, microencapsulation of powders improves flowability and reduces dust generation and formation of aggregates in the production process.

It is well known in the prior art to utilise spray drying techniques in encapsulation of a variety of core materials from photocopier dyes to agricultural and pharmaceutical ingredients. Natural and synthetic waxes and polymers have been used individually or in combination with each other in the formation of coated products utilising such techniques. The major advantage of spray drying microencapsulation over other encapsulation methods is the ease of application and the minimal number of processing steps required. However coats formed from spray drying in the prior art are typically porous and irregular, with roughened surfaces. Such core coatings lead to products with inferior flow properties, as well as coatings of reduced effectiveness. Such reduced effectiveness is of particular importance in the sustained release, enteric and taste masking applications. For example, in sustained release applications, it is critical to control coat permeability in order to provide selectivity in the release profile of the core material.

Accordingly, it is an object of the present invention to overcome, or at least alleviate, one or more of the difficulties related to the prior art.

Accordingly, in a first aspect of the invention

there is provided a taste-masked free-flowing powder including microcapsules having a particle size of approximately 300 µm or less, wherein each microcapsule includes an effective amount of

a core element including at least one pharmaceutically active ingredient; and

a substantially smooth and continuous microcapsule coating on the core element formed from a coating composition including a water insoluble polymer;

said coated microcapsules exhibiting a reduced dissolution profile.

The substantially smooth and continuous coat is substantially hole-free. The substantially smooth and continuous nature of the microcapsule coating may be achieved by spray drying from a suspension or dispersion of the pharmaceutically active ingredient in a solution of the coating composition in a solvent in a drying gas having a low dew point. The dew point may preferably be less than 0°C, more preferably less than approximately -15°C.

By "substantially smooth and continuous microcapsule coating" we mean a microcapsule coating which retains a smooth and continuous appearance when magnified 1000 times under a scanning electron microscope.

The microcapsules according to the present invention exhibit improved flow characteristics as well as an increase in the effectiveness of the coating. The coated microcapsules exhibit a reduced dissolution profile relative to a coating formed utilising standard microencapsulation methods.

The dissolution profile of the microcapsule composition may be reduced by approximately 25%, preferably approximately 40%, more preferably approximately 50%, relative to a standard microencapsulated form, when measured at a pH approximately that of the mouth, for example a pH of approximately 6.8 in the period from 0 to approximately 45 minutes, preferably 0 to approximately 20 minutes.

By "standard microencapsulation form" we mean a

microcapsule composition formed by spray drying from a suspension or dispersion of the pharmaceutically active ingredient in a solution of the coating composition in a solvent utilising ambient air as the drying gas.

By "dissolution profile" as used herein, we mean a plot of amount of active ingredient released as a function of time. The dissolution profile may be measured utilising the Drug Release Test (724) which incorporates standard test USPXXII 1990. (Test(711) Supplement VI, 1992). The dissolution tests are conducted in a modified flow through cell apparatus. A profile is characterised by the test conditions selected. Thus the dissolution profile may be generated at a preselected temperature, flow rate and pH of the dissolution media.

Preferably each microcapsule includes

approximately 90% to 10%, preferably 80% to 10% by weight, based on the total weight of the microcapsule composition of a core element including at least one pharmaceutically active ingreident; and

approximately 10 to 80%, preferably 20% to 90% by weight of a substantially smooth and continuous microcapsule coating on the core element formed from a coating composition including a water insoluble polymer.

The microcapsules have a particle size of approximately 300 µm or less, preferably less than 150 µm, more preferably approximately 75 µm to 150µm. The small particle size ensures that the particles have a substantially non-gritty feel in the mouth. The small particle size may also minimise break-up of the microcapsules in the mouth, e.g. by the teeth.

It has been found that a coat weight of at least approximately 20% by weight, based on the total weight of the microcapsules provides a further improvement in taste-masking.

The core element in the coated microcapsules according to the present invention may include at least approximately 75% by weight to 100% by weight of the pharmaceutically active ingredient.

The core element may be of any suitable particle

size. Particle sizes of approximately 0.1 to 250 µm have been found to be suitable. Particle sizes of less than 125 µm, preferably approximately 35 to 125 µm have been found to be particularly suitable.

Typical microcapsule coatings may be in the range of approximately 0.005 µm to 25 µm, preferably approximately 0.05 to 5 µm. It will be understood, accordingly, that the rate of absorption may be modified by modifying the thickness and/or the composition of the microcapsule coating.

The pharmaceutically active ingredient may be any compound which may be utilised in a taste-masked, sustained release or delayed release treatment.

The pharmaceutically active ingredient may be selected from any one or more of the following.

Analgesics including acetaminophen (paracetamol).

Bronchodilators including theophylline.

Antihistamines including Azatadine maleate, Brompheniramine maleate, Carbinoxamine maleate, Chlorpheniramine maleate, Dexchlorpheniramine maleate, Diphenhydramine HCl, Doxylamine succinate, Methdilazine HCl, Promethazine, Terfenadine, Trimeprazine Tartrate, Tripelennamine citrate, Tripelennamine HCl, Tripolidine HCl.

Antibiotics including Penicillin V Potassium, Cloxacillin sodium, Dicloxacillin sodium, Nafcillin sodium, Oxacillin sodium, Carbenicillin Indanyl Sodium, Oxytetracycline HCl, Tetracycline HCl, Clindamycin Phosphate, Clindamycin HCl, Clindamycin Palmitate, Lincomycin HCl, Novobiocin Sodium, Nitrofurantoin Sodium, Metronidazole, Metronidazole hydrochloride.

Antituberculosis Agents including Isoniazid.

Cholinergic Agents including Ambenonium chloride, Bethanecol Chloride, Neostigmine bromide, Pyridostigmine bromide.

Antimuscarinics including Anisotropine methylbromide, Clidinium bromide, Dicyclomine HCl, Glycopyrrolate, Hexocyclium methylsulfate, Homatropine methylbromide, Hyoscyamine sulphate, Methantheline

bromide, Hyoscine hydrobromide, Oxyphenonium bromide, Propantheline bromide, Tridihexethyl chloride.

Sympathomimetics including Bitolterol Mesylate, Ephedrine, Ephedrine HCl, Ephedrine sulphate, Orciprenaline sulphate, Phenylpropanol amine hydrochloride, Pseudoephedrine hydrochloride, Ritodrine hydrochloride, Salbutamol sulphate, Terbutaline sulphate.

Sympatholytic Agents including Phenoxybenzamine hydrochloride.

Miscellaneous Autonomic Drugs including Nicotine.

Iron Preparations including Ferrous gluconate, Ferrous sulphate.

Haemostatics including Aminocaproic acid.

Cardiac Drugs including Acebutolol HCl, Diltiazem hydrochloride, Disopyramide phosphate, Flecainide acetate, Procainamide hydrochloride, Propranolol hydrochloride, Quinidine Gluconate, Timolol maleate, Tocainide hydrochloride, Verapamil hydrochloride.

Antihypertensive Agents including Captopril, Clonidine hydrochloride, Doxazosin Mesylate, Hydralazine hydrochloride, Mecamylamine hydrochloride, Metoprolol tartrate, Prazosin Hydrochloride.

Vasodilators including Papaverine hydrochloride.

Non-Steroidal Antiinflammatory Agents including Choline salicylate, Magnesium salicylate, Meclofenamate sodium, Diclofenac sodium, Naproxen sodium, Tolmetin sodium, Ibuprofen, Ketoprofen, Fenoprofen.

Opiate Agonists including Codeine HCl, Codeine phosphate, Codeine sulphate, Dextromoramide tartrate, Hydrocodone bitartrate, Hydromorphone hydrochloride, Pethidine hydrochloride, Methadone hydrochloride, Morphine sulphate, Propoxyphene hydrochloride.

Anticonvulsants including Phenobarbital sodium, Phenytoin sodium, Troxidone, Ethosuximide, Valproate sodium.

Tranquilizers including Acetophenazine maleate, Chlorpromazine hydrochloride, Fluphenazine hydrochloride, Masoridazine mesylate, Prochlorperazine and its salts, Promazine hydrochloride, Thioridazine hydrochloride,

Trifluoroperazine hydrochloride, Lithium citrate, Molidone hydrochloride, Thiothixine hydrochloride.

Stimulants including Benzphetamine hydrochloride, Dextroamphetamine sulphate, Dextroamphetamine phosphate, Diethylpropion hydrochloride, Fenfluramine hydrochloride, Methamphetamine hydrochloride, Methylphenidate hydrochloride, Phendimetrazine tartrate, Phenmetrazine hydrochloride, Caffeine citrate.

Barbiturates including Amylobarbitone sodium, Butabarbital sodium, Secobarbital sodium;, Sedatives including, Hydroxyzine hydrochloride, Methyprylon.

Expectorants including Potassium Iodide.

Antiemetics including Benzquinamide hydrochloride, Metoclopramide HCl, Trimethobenzamide hydrochloride.

GI Drugs including Ranitidine Cimetidine, Famotidine and suitable salts thereof.

Heavy Metal Antagonists including Penicillamine, Penicillamine HCl.

Antithyroid Agents including Methimazole.

Genitourinary Smooth Muscle Relaxants including Flavoxate hydrochloride, Oxybutynin chloride.

Vitamins including Thiamine hydrochloride, Ascorbic acid.

Unclassified Agents including Amantadine hydrochloride, Colchicine, Etidronate disodium, Leucovorin calcium, Methylene blue, Potassium chloride, Pralidozime chloride, Potassium Ascorbate, Sodium Ascorbate, Calcium Ascorbate, Nicotine salts.

All Oral Penicillins
Oral Cephalosporins
Oral Aminoglycosides
Oral Macrolides
Oral Monobactams
Oral Rifamycin analogues
Oral Tetracyclines
Oral Penems
Oral Peptide antibiotics.

The pharmaceutically active ingredient may be in

the form of a salt.

The microcapsule composition according to the present invention is particularly suitable for utilisation with analgesics such as acetaminophen, bronchodilators such as theophylline, H_2 receptor antagonists such as ranitidine hydrochloride and non-steroidal anti-inflammatory drugs (NSAIDS). The microcapsule composition may be applied to active ingredients having a crystalline or granulate morphology. A crystalline morphology is preferred. The active ingredient may have an aspect ratio of approximately 1:1.

The taste-masked microcapsule powder composition may be provided in any suitable unit dosage form. The pharmaceutical composition may be provided in a form selected from sprinkles, sachets, chewing gums, tablets; including chewable tablets, gums, lozenges, liquids, suspensions, injectables, implantables, inhalants, filled capsules; including filled gelatin capsules. The pharmaceutical composition may be provided in the form of dispersible or effervescent tablets.

The microcapsule coating according to the present invention may take any suitable form depending upon the release profile required. The coating composition from which the microcapsule coating is formed includes a water insoluble polymer component.

The water insoluble polymer may be selected from ethyl cellulose or dispersions of ethyl cellulose such as those sold under the trade designation Aquacoat or Surelease, acrylic and/or methacrylic ester polymers, cellulose acetates, butyrates or propionates or copolymers of acrylates or methacrylates having a low quaternary ammonium content and biodegradable polymers.

The water insoluble (matrix) polymer may be present in the coating composition in an amount of from approximately 40 to 100% by weight, preferably 50 to 80% by weight based on the dry weight of the microcapsule coating.

The solvent which may be used in the preparation of the coating of the microcapsule composition may be an

organic solvent. The solvent may be such that it constitutes a good solvent for the microcapsule coating composition but is substantially a non-solvent or poor solvent for the pharmaceutically active ingredient. Whilst the active ingredient may partially dissolve in the solvent, in this aspect of the invention, the active ingredient will precipitate out of the solvent during the spray drying process much more rapidly than the microcapsule coating composition.

The solvent may be selected from alcohols such as methanol, ethanol, halogenated hydrocarbons such as dichloromethane (methylene chloride), hydrocarbons such as cyclohexane, ketones, esters, ethers and aldehydes and mixtures thereof. Dichloromethane has been found to be particularly suitable. The solvent may be present in amounts of from approximately 25-97% by weight preferably 70-95% by weight based on the total weight of the microcapsule coating composition.

Accordingly, the taste-masked microcapsule coating composition may include

approximately 3% to 75% by weight based on the total weight of the coating composition of a water insoluble polymer;

0 to approximately 72% by weight of a polymeric component selected from one or more of an enteric polymer, an acid-soluble (reverse enteric) polymer, and a partially water soluble polymer; and

approximately 25% to approximately 97% by weight of an organic solvent.

Where the microcapsule coating is an enteric coating, the enteric polymer may be selected from cellulose acetate phthalate, hydroxypropyl methylcellulose phthalate (HPMCP), polyvinyl acetate phthalate, methacrylic acid copolymer, hydroxypropyl methylcellulose acetate succinate, shellac, cellulose acetate trimellitate and the like or mixtures thereof. Particularly preferred enteric polymers include semi-synthetic or synthetic resins bearing carboxyl groups.

The enteric polymer may be present in the coating

in an amount of from approximately 3 to 96% by weight, preferably approximately 5% to 75% by weight, based on the dry weight of the coating.

Where the microcapsule coating is a sustained release coating, the coating may include

approximately 40% to 100% by weight, preferably 50% to 97%, based on the dry weight of the microcapsule coating of a water insoluble polymer;

0 to approximately 50% by weight, preferably 3% to 25%, of an enteric polymer; and

0 to approximately 50% by weight, preferably 3% to 25%, of a partially water soluble component.

The partially water-soluble component may be selected from natural or synthetic waxes, polymers such as polyvinylpyrrolidone, hydroxypropyl cellulose, hydroxypropyl methylcellulose, polyethylene glycol, polyvinyl alcohol or monomers such as sugars, salts, or organic acids and mixtures thereof.

In a further aspect of the present invention, the coating composition may function to produce a modified release coat. The modified release for example may provide substantially no or a slow rate of release at alkaline pH, for example as encountered in the mouth of the patient, but substantially immediate or more rapid rate of release at acid pH, for example as encountered in the stomach of the patient.

Accordingly, the modified release core coating may include

approximately 20% to 97% by weight based on the dry weight of the microcapsule coating of a water insoluble polymer;

approximately 3% to 80% by weight of an acid-soluble (reverse enteric) polymer; and

0 to approximately 40% by weight of a partially water soluble component.

The water insoluble polymer of the modified release core coating may be present in amounts of from approximately 20 to 50% by weight, more preferably 35 to 45% by weight, based on the total weight of the

microcapsule composition excluding weight of filler.

The reverse enteric polymer may be selected for example from the acrylate copolymer sold under the trade designation Eudragit E100, or natural polymers such as Chitin and the polyvinyl ester polymer sold under the trade designation AEA (polyvinyl acetal diethylamino acetate) by Sankyo Pharmaceuticals. The acrylate copolymer Eudragit E-100 is preferred.

The reverse enteric polymer may be present in amounts of from approximately 10 to 75% by weight, more preferably 15% to 50% by weight based on the dry weight of the microcapsule coating.

The coating composition according to this aspect of the present invention may further include at least one plasticiser.

The plasticiser may be selected from diethyl phthalate, triethyl citrate, triethyl acetyl citrate, triacetin, tributyl citrate, polyethylene glycol, glycerol, dibutylsebacate, castor oil and the like.

The plasticiser may be present in amounts of from 0 to approximately 50% by weight based on the total weight of the microcapsule coating, excluding filler.

The microcapsule compostion may further include carriers or excipients, fillers, flavouring agents, stabilizing agents and colourants. Suitable fillers may be selected from insoluble materials such as silicon dioxide, titanium dioxide, talc, alumina, starch, kaolin, polacrilin potassium powdered cellulose, and microcrystalline cellulose and mixtures thereof. Soluble fillers may be selected from mannitol, sucrose, lactose, dextrose, sodium chloride, sorbitol and mixtures thereof.

The filler may be present in amounts up to approximately 75% by weight based on the total weight of the microcapsule composition.

As stated above, the microcapsule composition according to the present invention is applicable to pharmaceutically active ingredients having a crystalline morphology and particularly a low aspect ratio. The release rates may be more rapid if the aspect ratio is

high. Similarly, where the pharmaceutically active ingredient exhibits high water or organic solvent solubility, the release rates may be more rapid than is required in a particular application.

Accordingly in a preferred form the core element may include approximately 10% to 95% by weight, preferably 75% to 95% by weight of a pharmaceutically active ingredient; and

approximately 5% to 90% by weight of a supplementary component selected from waxes, acids, bases, water insoluble polymers, enteric polymers, and partially water soluble polymers and other suitable pharmaceutical excipients.

The supplementary component may be provided as an intimate mixture with the active ingredient or as a precoat thereon. Where an intimate mixture is formed, polymers such as hydroxypropyl methyl cellulose may be used.

Where a precoat is formed, a wax coat is preferred. A paraffin wax may be used. In a preferred form the active ingredient is a compound of high water or solvent solubility and the supplementary component forms a precoat on the active ingredient.

By "high water or solvent solubility", we mean solubility of greater than 1 in 30.

Alternatively, where release rates are more rapid than required, the microcapsules according to the present invention may include an overcoat layer. The overcoat layer may have a similar composition to the precoat layer described above.

The core elements may be formulated utilising an aqueous or organic solvent of the type described above.

As stated above, the substantially smooth and non-porous microcapsule coating according to the present invention may be provided by forming and drying the microcapsule coating in an atmosphere modified to reduce evaporation rates. Preferably, this is achieved by drying in the presence of a controlled concentration of a solvent for the microcapsule coating.

Accordingly, in a further aspect of the present invention there is provided a process for preparing a taste-masked free-flowing powder including microcapsules having a particle size of approximately 300 μm or less, and including an effective amount of a core element including at least one pharmaceutically active ingredient; and

a substantially smooth and continuous microcapsule coating on the core element formed from a coating composition including a water insoluble polymer;

said microcapsule coating exhibiting reduced dissolution profile;

which process includes

providing a sufficient amount of

at least one pharmaceutically active ingredient;

a solution of a coating composition including

a water insoluble polymer; and

an organic solvent therefor;

suspending or dispersing the pharmaceutically active ingredient in the coating solution; and

spray-drying the suspension or dispersion in a drying gas having a low dew point, to form microcapsules.

The dew point may preferably be less than 0°C, more preferably less than approximately -15°C.

Preferably, the drying chamber includes a controlled amount of the solvent.

Preferably, for a solvent such as methylene chloride, the solvent concentration in the drying chamber is maintained above 40,000 parts, more preferably in the range of approximately 40,000 to 100,000 parts per million of organic solvent.

The spray-drying process for such solvents may be conducted at a process temperature of from approximately 5°C to 15°C.

The utilisation of a drying gas exhibiting a low dew point aids the production of a substantially smooth and continuous coating. It has also been found that the presence of a solvent during the drying step slows the

evaporation rate of the solvent such that a substantially smooth and continuous coat exhibiting reduced permeability is produced. The concentration of non-solvent e.g. water present should be kept very low and that, in combination with the controlled drying conditions, results in microcapsules with smooth and continuous coats. These two factors may be interrelated. Thus the higher the drying gas dew point, the higher the solvent vapour pressure required in the system to give a substantially smooth coat.

The drying process may be of any suitable type.

Spray drying of microencapsulated powders may be undertaken utilising either rotary, pneumatic or pressure atomisers located in either a co-current, counter-current or mixed-flow spray dryer or variations thereof. The nature of the spray drying chamber is not critical. However the chamber should be substantially free of precipitant or non-solvent during processing.

In one form of this aspect of the present invention, the drying gas may be partially saturated with solvent vapour. Accordingly the drying step according to this aspect of the present invention may include

introducing the microcapsule formulation into a spray dryer through an atomising device; and

passing a drying gas containing a controlled amount of a suitable solvent therefor, through the spray drying chamber.

The drying gas may be of any suitable type. Nitrogen or air may be used. The air should be substantially dry and pure. It has been found that the dryness of the drying gas and/or atomising gas may affect the quality of the microcapsule coat formed. The drying gas dew point is preferably less than -15°C. The drying gas dew point may more preferably be maintained in the range of from approximately -25°C to -30°C. The atomising gas may be the same as, or similar to, the drying gas.

The drying gas may be heated or cooled to control the rate of drying. A temperature below the boiling point of the solvent may be used. A process temperature in the

range of approximately 5 to 15°C, preferably approximately 5 to 8°C, may be used. Inlet temperatures will typically be in the range of from approximately 20°C to 60°C and outlet temperatures approximately 5°C to 20°C. Control of temperature may also affect the quality of microcapsule coat formed.

The coating solvent utilised in the drying step may be the same or a different solvent to that used in the microcapsule coating composition. Desirably the same solvent is used in each case. The solvent may be a pharmaceutically acceptable organic solvent.

The amount of solvent introduced during the drying step is dependent upon the form of coating required. Thus the solvent vapour pressure may be controlled to ensure the formation of a smooth microcapsule coating is formed.

The present invention permits the optimisation of the coat formation to meet the needs of the material or application. Adjusting the microcapsule coating composition allows modification of the release profile for the material. Controlling the process parameters including temperature, solvent concentration, spray dryer capacity, atomising air pressure, droplet size, viscosity, total air pressure in the system and solvent system, allows the formation of a range of coats, ranging from dense, continuous, non-porous coats through to more porous microcapsule/polymer matrices.

In accordance with a further aspect of the present invention there is provided a method of treating a patient, which method includes administering to a patient a therapeutically or prophylactically effective amount of a taste-masked free-flowing powder including microcapsules having a particle size of approximately 300 μm or less, wherien each microcapsule includes

approximately 80% to 10% by weight, based on the total weight of the microcapsule composition of a core element of at least one pharmaceutically active ingredient; and

approximately 20% to approximately 90% by weight of a substantially smooth and continuous microcapsule

coating on the core element formed from a coating composition including a water insoluble polymer;

said microcapsule coating exhibiting a reduced dissolution profile.

Preferably the pharmaceutically active ingredient is selected from analgesics such as acetaminophen, bronchodilators such as theophylline, H_2 receptor antagonists such as ranitidine hydrochloride and non-steroidal anti-inflammatory drugs (NSAIDS).

More preferably the pharmaceutically active ingredient is selected from analgesics, bronchodilators, H_2 receptor antagonists and non-steroidal anti-inflammatory drugs.

The method of treatment according to this aspect of the present invention is particularly applicable where careful control of the release rate of the pharmaceutically active ingredient is required and the active ingredient exhibits an unpleasant taste.

The present invention will now be more fully described with reference to the accompanying examples and drawings. It should be understood, however, that the following description is illustrative only and should not be taken in any way as a restriction on the generality of the invention specified above.

EXAMPLES

The material to be encapsulated is suspended in a solution of the coating material dissolved in a suitable solvent. The suspension may be dried in any commercially available spray dryer in the usual manner. The process is modified such that the drying environment is partially saturated with solvent. The process is conducted at temperatures below the normal boiling point of the solvent in a controlled environment. The drying environment may be pre-loaded with solvent which reduces its evaporative capacity and drying rates are therefore reduced. The extent to which evaporation rates are decreased is determined by the dew point, temperature and the vapour concentration of the drying environment. The slower the evaporation rates the denser the membranes with rapid

evaporation producing porous membranes. Solvent vapour concentration should be kept below a critical value wherein the atomised droplets do not dry sufficiently, otherwise an immobile adherent mass will be formed. The concentration must be high enough however, to allow the dense, non porous films to be formed.

Microencapsulation may be conducted using a commercially available spray dryer, e.g. a Niro Mobile spray dryer, using standard techniques. The spray dryer should be of such dimension to allow sufficient residence time for controlled drying. In a further option, spray guns with various size nozzles may be used to control the drying process. Atomising pressure (at the nozzle) may range between approximately 40 and 500 kPa. Flow rates of fluid suspension to the atomiser may be varied between approximately 20 and 60 mL/min. Powder should be collected in such a manner as to minimise damage to the microcapsules. In this case it is collected from the walls of the drying chamber by means of an air wand.

Determination of Release Rates from Microcapsules

Release rates of microcapsulated pharmaceutical active ingredients are most readily determined by means of a modified flow through cell apparatus and at a temperature of 37°C ± 0.5°C. Dissolution medium is recycled via a 900 mL reservoir maintained at 37°C ± 0.5°C which is continuously stirred. Samples are withdrawn from the reservoir at set time intervals and analysed for microcapsule material. Dissolutions are typically performed at pH 1.2, 6.8 or 7.5.

EXAMPLE 1

(a) Microencapsulated Acetaminophen with delayed release

Component	Mass
Ethylcellulose	16g
Eudragit E100	4g
Paracetamol 75-125 µm	20g
Methylene chloride	270g

The ethylcellulose had a viscosity grading according to the manufacturer of 10 cps. The acetaminophen was sieved to give greater than 95% in the range 75 µm

to 125 µm.

Acetaminophen was dispersed in a solution of ethyl cellulose in dichloromethane and sprayed dry with the chamber partially saturated with methylene chloride and maintained above 40,000 ppm at an inlet air temperature maintained at 20°C and the outlet air temperature varies between 5°C and 8°C during the spray drying.

A free flowing white powder was produced with none of the taste of acetaminophen. Dissolution testing confirmed the pH dependence of release. This is illustrated in Figure 1. This profile indicates that the product will have adequate protection in the mouth but will release rapidly in contact with gastric fluid. >95% released in 5 min. at pH 1.2. <30% released in 40 min. at pH 6.8.

(b) Microencapsulated Acetaminophen with delayed release

Component	Mass
Ethylcellulose	20g
Eudragit E100	2g
Paracetamol 75-125 µm	20g
Methylene chloride	270g

Sprayed dry under similar conditions as in Example 1(a) to control temperature, vapour concentration and evaporation rate.

A free flowing white powder was produced with none of the taste of acetaminophen. Dissolution testing confirmed the pH dependence of release. This is illustrated in Figure 2. This profile indicates that the product will have adequate protection in the mouth but will release rapidly in contact with gastric fluid. However dissolution is less rapid at pH 1.2 than in Example 1(a). Approximately 75% released in 45 min. at pH 1.2. <30% released in 40 min. at pH 6.8 and confirms the influence of formulation on overall release rates.

EXAMPLE 2

Sustained Release Theophylline

Ethylcellulose	20 g
Polyethylene glycol 6000	5 g
Theophylline	20 g
Dichloromethane	258 g

Sprayed dry under similar conditions as Example 1(a) to control temperature, vapour concentration and evaporation rate.

A free flowing white powder was produced with none of the taste of theophylline. Dissolution testing showed pH independent release at a constant rate of 15% per hour.

EXAMPLE 3

Enteric Coated Diclofenac

Ethylcellulose	20 g
HPMCAS-HF*	4 g
Sodium Diclofenac	20 g
Dichloromethane	258 g

* Hydroxypropyl methylcellulose acetate succinate - HF grade.

Sprayed dry under similar conditions as used in Example 1(a) to control temperature, vapour concentration and evaporation rate.

A free flowing white powder was produced. Dissolution testing showed a typical enteric release profile. This is illustrated in Figure 3.

EXAMPLE 4

A series of microcapsule compositions were prepared utilising the active ingredients 1 and 2 listed below.

The process for preparation is similar for each active ingredient and is as follows:

Active	20 g
Ethylcellulose (EC)	20 g
Methylene Chloride (CH_2Cl_2)	200 g

The actives tested include Paracetamol, Ranitidine HCl, Doxycycline HCl, Pseudoephedrine, HCl, Naproxen Na, Theophylline, Apsirin.

(1) The active ingredient was seived to 75 to 125 μm in size prior to its dispersion in the CH_2Cl_2/EC solution.

(2) The resulting suspension was sprayed under standard conditions, that is dry air (dew point <-15°C) at a process temperature of 5 to 8°C. The spray was conducted in a Mobile Minor Niro

spray dryer at similar rates and atomising air pressures as in Example 1.

It is noted that (a) solubility of the active ingredient, and (b) the crystal morphology (crystalline vs granulate) ultimately affect the release rates of the product. Additionally, the aspect ratio (length/breadth) of crystalline materials is also important.

From a comparison of the solubilities of actives and release rates of product with simple ethylcellulose coat, it appears that the less soluble actives are released slower than more soluble ones. Similarly, where the active is in the form of a granule instead of a crystal, inadequate coverage may be obtained leading to higher release rates. To slow the release rates of the more soluble or granular actives, further components may optionally be added to the microcapsules.

For all of the actives there was some degree of tastemasking.

Table 1 indicates the relative solubilities of the various actives in water and in chloroform. The solubility in chloroform is used as an approximation of solubility in methylene chloride and therefore to predict how the active may respond in the coating suspension.

TABLE 1

Active	Aqueous Solubility (approx.)	Chloroform Solubility (approx.)
Ranitidine HCl	1/1-10	insoluble
Doxycycline HCl	1/3	insoluble
Pseudoephedrine HCl	1/1.6	1/60
Naproxen Na	1/10-30	insoluble
Paracetamol	1/70	1/50
Theophylline	1/120	1/200
Aspirin	1/300	1/17

Table 2 indicates the crystal morphology. Where needles are used, release from granules is generally faster than that from crystals of the same active.

TABLE 2

Crystal Morphologies of Exemplary Actives for Microencapsulation Process

Active	Morphology	Aspect Ratio
Doxycycline HCl	Crystalline	2:1
Pseudoephedrine HCl	Crystalline needles	5:1
Theophylline	Crystalline needles	6:1
Aspirin	Granulate	1:1
Naproxen Na	Granulate	1.5:1
Paracetamol	Crystalline	1:1
Ranitidine HCl	Granulate	1:1

Figure 4 is a dissolution profile graph showing a total of seven actives with simple ethylcellulose membranes. The dissolutions were conducted at pH 6.8 in flow through cells.

EXAMPLE 5

(a) Example 1 was repeated utilising the following composition

Component	Mass
Ethyl Cellulose	8 g
Paracetamol (within 175 to 250 µm)	20 g
Methylene Chloride	100 g

(b) For comparison purposes, Example 5 was repeated utilising ambient air only as the drying gas.

Results achieved are illustrated in Figures 5(a) and (b) and Figure 6.

Figures 5(a) and (b) illustrate the variation in coat smoothness and apparent coat porosity due to evaporation rate variation.

Figure 6 illustrates the relative release rates achieved utilising ambient air and air maintained at a dew point below -15°C. Release rates at pH 6.8, for example after 20 min are approximately 50% less utilising the process of the present invention.

EXAMPLE 6 (Comparative)

In this example, the feed mixture to the spray

dryer was composed of the following materials.

Component	Mass %
Acetaminophen	14.00
Ethyl Cellulose	5.00
Methylene Chloride	81.00

The ethyl cellulose was dissolved in the methylene chloride contained in a stainless steel mixing vessel. The acetaminophen was then dispersed with mixing and transferred to the feed tank of the Niro Portable Spray Dryer.

The spray dryer was operated with a feed rate of 32 grams per minute utilising a centrifugal wheel atomiser. The drying gas used was ambient air. The air inlet heater was set to produce an air outlet temperature of 25°C to 30°C. The air pressure was 4.8 bar.

The resultant product was viewed under a scanning electron microscope. The results are illustrated in Figures 7(a) and (b). The product exhibited little taste-masking consistent with the porous structure of Figures 7(a) and (b).

EXAMPLE 7

A series of microcapsule products utilising Ranitidine, a highly water soluble active were prepared in accordance with the process of the present invention. A number of modifications were made to the core or microcapsule coat to reduce dissolution rate as follows:

(1) Polymer coating alone (as previously described).

(2) Wax sealing of polymer coated microcapsules.

- Ranitidine microcapsules (from Example above)	3g
- 10% Paraffin solution in cyclohexane	50g

Paraffin solution poured over bed of microcapsules held on porous support. Excess wax solution removed and the microcapsules were dried. Product showed a reduced release rate in comparison to the polymer only microcapsules (Figure 8) and less of the taste of ranitidine HCl.

(3) Polymer coating after wax sealing of ranitidine

granules.

(a) Wax Sealing

- Hard Paraffin wax 7.5 g
- Ranitidine HCl 20 g
- Methylene chloride 300 g

Ranitidine was suspended in the wax solution and spray dried in the conventional manner with an outlet temperature of 15°C. The product was free flowing, but demonstrated minimal taste masking and a high in vitro dissolution rate in pH 6.8 phosphate buffer.

(b) Polymer Coating

The product from (a) above was resuspended in a chilled (5°C) methylene chloride solution of ethylcellulose and spray dried again employing the usual process conditions.

- Wax sealed ranitidine HCl 10 g
- Ethylcellulose N10 10 g
- Methylene chloride 100 g

Outlet temperature was 5°C.

Figure 8 shows a substantial decrease in the in vitro release rate consistent with improved taste masking.

EXAMPLE 8

A series of core formulations were prepared utilising ranitidine HCl as the active ingredient to illustrate further modifications to the core to reduce dissolution rates.

(1) Ranitidine HCl 50 g
Purified water 100 g

Ranitidine was dissolved and spray dried using a Niro Mobile Minor spray dryer. Inlet air temperature was set at 130°C giving an outlet temperature of 35 to 45°C at a spray rate of 70 mL/min.

A free flowing off-white powder was recovered from the walls of the drying chamber and the cyclone receiver jar. Microscopically the powder was small spherical beads suitable for subsequent

polymer coating by the standard method described previously.

(2)	Ranitidine HCl	50 g
	Hydroxypropyl methylcellulose*	5 g
	Purified water	100 g

[*Pharmacoat 615]

Five percent HPMC was added as a binder/thickening agent to increase the particle size of the product. The ranitidine HCl and HPMC were dissolved and the viscous solution spray dried under the same conditions described above.

(2)	Ranitidine HCl	50 g
	Hydroxypropyl methylcellulose	5 g
	$CaCO_3$ (fine)	10g
	Purified water	100 g

$CaCO_3$ was incorporated in the formulation to act as a "seed core" around which the active material could be precipitated.

The formulation was spray dried under the same conditions described above.

The product was collected as before. Microscopically the spherical beads showed none of the central voids seen in the previous examples. The absence of central voids reduces mechanical damage during tabletting and subsequent chewing.

Finally, it is to be understood that various other modifications and/or alterations may be made without departing from the spirit of the present invention as outlined herein.

Claims

1. A taste-masked free-flowing powder including microcapsules having a particle size of approximately 300 µm or less, wherein each microcapsule includes an effective amount of

a core element including at least one pharmaceutically active ingredient; and

a substantially smooth and continuous microcapsule coating on the core element formed from a coating composition including a water insoluble polymer;

said coated microcapsules exhibiting a reduced dissolution profile.

2. A taste-masked free-flowing powder according to Claim 1, wherein the dissolution profile of the coating is reduced by approximately 25% relative to a standard microencapsulated form.

3. A taste-masked free-flowing powder according to Claim 1, wherein the microcapsules have a particle size of less than approximately 150 µm.

4. A taste-masked free-flowing powder according to Claim 1, wherein the core element includes at least approximately 75% by weight of the pharmaceutically active ingredient.

5. A taste-masked free-flowing powder according to Claim 1, wherein the pharmaceutically active ingredient is selected from analgesics, bronchodilators, H_2 receptor antagonists and non-steroidal anti-inflammatory drugs.

6. A taste-masked free-flowing powder according to Claim 5, wherein the active ingredient is selected from acetominophen, ranitidine, doxycycline, pseudoephedrine, naproxen and theophylline and salts thereof.

7. A taste-masked free-flowing powder according to Claim 1, wherein the coating composition includes a major proportion of ethyl cellulose.

8. A taste-masked free-flowing powder including microcapsules having a particle size of approximately 300 µm or less, wherein each microcapsule includes

approximately 90% to 10% by weight, based on the total weight of the microcapsule composition of a core

element including at least one pharmaceutically active ingreident; and

approximately 10 to 90% by weight of a substantially smooth and continuous microcapsule coating on the core element formed from a coating composition including a water insoluble polymer.

9. A taste-masked free-flowing powder according to Claim 1, wherein the coating composition includes

approximately 3% to 75% by weight based on the total weight of the coating composition of a water insoluble polymer;

0 to approximately 72% by weight of a polymeric component selected from one or more of an enteric polymer, an acid-soluble (reverse enteric) polymer, and a partially water soluble polymer; and

approximately 25% to 97% by weight of an organic solvent.

10. A taste-masked free-flowing powder according to Claim 1, wherein the microcapsule coating includes

approximately 40% to 100% by weight based on the dry weight of the microcapsule coating of a water insoluble polymer;

approximately 0 to 50% by weight of an enteric polymer; and

0 to approximately 50% by weight of a partially water soluble component.

11. A taste-masked free-flowing powder according to Claim 1, wherein the microcapsule coating includes

approximately 20% to 97% by weight based on the dry weight of the microcapsule coating of a water insoluble polymer;

approximately 3 to 80% by weight of an acid-soluble (reverse enteric) polymer; and

0 to approximately 40% by weight of a partially water soluble component.

12. A taste-masked free-flowing powder according to Claim 1, wherein the microcapsule coating is formed by spray drying from a suspension or dispersion of the pharmaceutically active ingredient in a solution of the

coating composition in a solvent in a drying gas having a low dew point.

13. A taste-masked free-flowing powder according to Claim 12, wherein the solvent is selected from alcohols halohydrocarbons, hydrocarbons, and mixtures thereof.

14. A taste-masked free-flowing powder according to Claim 1, wherein the core element includes

approximately 10% to 95% by weight of a pharmaceutically active ingredient; and

approximately 5% to 90% by weight of a supplementary component selected from waxes, acids, bases, water insoluble polymers, enteric polymers, and partially water soluble polymers.

15. A taste-masked free-flowing powder according to Claim 14 wherein the pharmaceutically active ingredient is a compound of high aqueous or solvent solubility and the supplementary component forms a precoat on the active ingredient.

16. A taste-masked free-flowing powder according to Claim 15 wherein the pharmaceutically active ingredient is a ranitidine and the precoat is formed from a wax.

17. A taste-masked free-flowing powder according to Claim 1 wherein each microcapsule further includes an overcoat on the microcapsule coating formed from a supplementary component selected from waxes, water insoluble polymers, enteric polymers, and partially water soluble polymers.

18. A process for preparing a taste-masked free-flowing powder including microcapsules having a particle size of approximately 300 µm or less, and including an effective amount of

a core element including at least one pharmaceutically active ingredient; and

a substantially smooth and continuous microcapsule coating on the core element formed from a coating composition including a water insoluble polymer;

said microcapsule coating exhibiting reduced dissolution profile;

which process includes

providing a sufficient amount of

at least one pharmaceutically active ingredient;

a solution of a coating composition including

a water insoluble polymer; and

an organic solvent therefor;

suspending or dispersing the pharmaceutically active ingredient in the coating solution; and

spray-drying the suspension or dispersion in a drying gas having a low dew point to form microcapsules.

19. A process according to Claim 18 wherein the drying chamber includes a controlled amount of the solvent.

20. A process according to Claim 19, wherein the solvent concentration in the drying gas is maintained in the range of approximately 40,000 ppm or more.

21. A process according to Claim 20, wherein the spray-drying process is conducted at a process temperature of from approximately 5°C to 15°C.

22. A process according to Claim 21, wherein the water insoluble polymer includes a major proportion of ethyl cellulose, and the solvent includes methylene chloride.

23. A method of treating a patient, which method includes administering to the patient a therapeutically or prophylactically effective amount of a taste-masked free-flowing powder including microcapsules having a particle size of approximately 300 µm or less, wherein each microcapsule includes an effective amount of

a core element including at least one pharmaceutically active ingredient; and

a substantially smooth and continuous microcapsule coating on the core element formed from a coating composition including a water insoluble polymer;

said microcapsule coating exhibiting a reduced dissolution profile.

24. A method according to Claim 23 wherein each microcapsule includes

approximately 3% to 75% by weight based on the total weight of the coating composition of a water

insoluble polymer;

0 to approximately 72% by weight of a polymeric component selected from one or more of an enteric polymer, an acid-soluble (reverse enteric) polymer, and a partially water soluble polymer.

25. A method according to Claim 24, wherein the pharmaceutically active ingredient is selected from analgesics, bronchodilators, H_2 receptor antagonists and non-steroidal anti-inflammatory drugs.

26. A method according to Claim 25, wherein the pharmaceutically active ingredient is selected from acetominophen, ranitidine, doxycycline, pseudoephedrine, naproxen and theophylline or salts thereof.

27. A taste-masked free-flowing powder according to Claim 1, substantially as hereinbefore described with reference to any one of examples 1 to 5 and 7 to 8.

28. A taste-masked free-flowing powder according to Claim 1, in the form selected from sprinkles, sachets, chewing gums, tablets; including chewable, dispersible or effervescent tablets, gums, lozenges, liquids, suspensions, injectables implantables, inhalants, filled capsules; including filled gelatin capsules.

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FIGURE 1

GRAPH OF % PARACETAMOL RELEASED vs TIME
[pH 6.8, pH1.2]

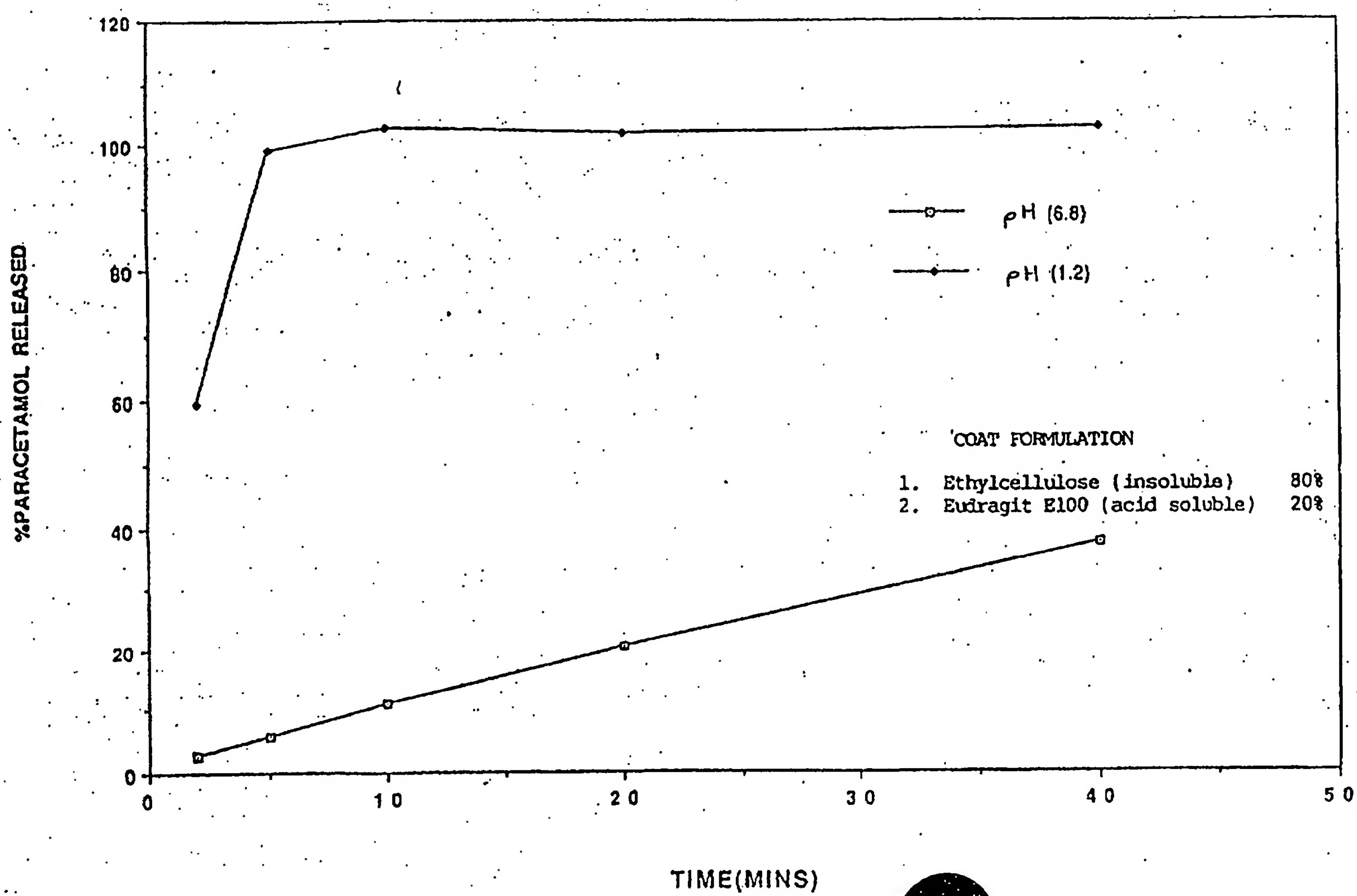

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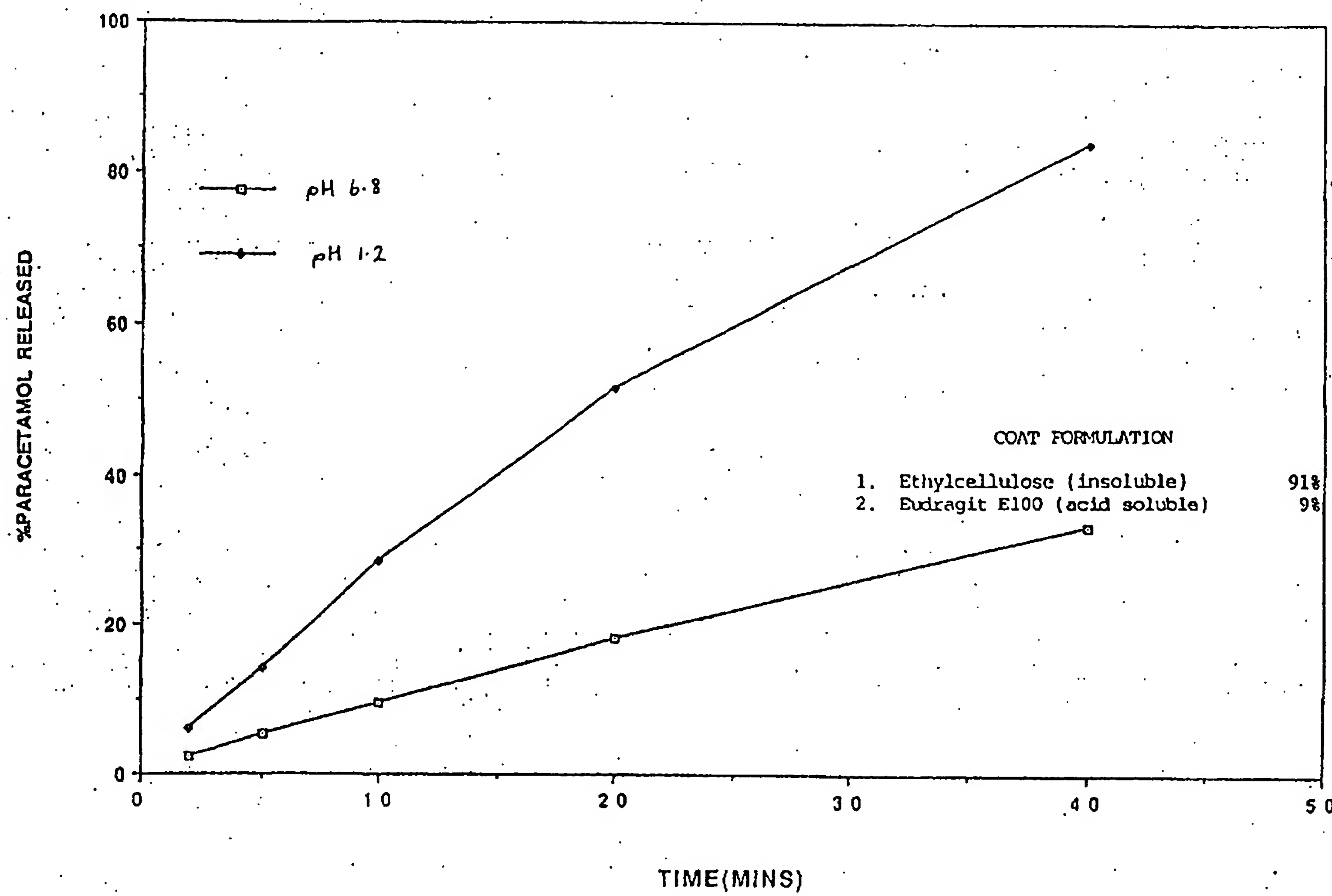
FIGURE 2

GRAPH OF % PARACETAMOL RELEASED vs TIME
(pH 6.8, pH 1.2)



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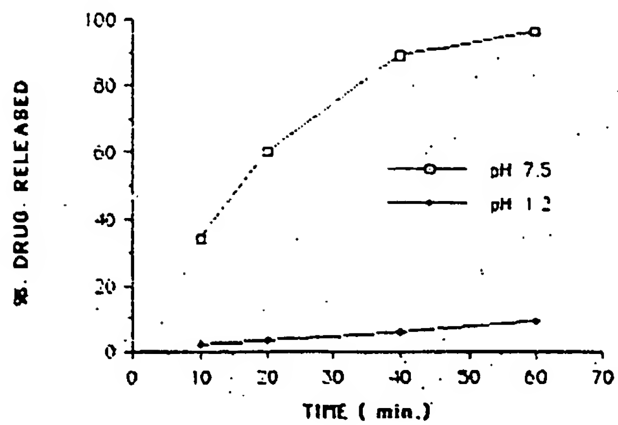
100
80
60
40
20
0
% DRUG RELEASED
0
10
20
30
40
50
60
70
TIME (min.)
pH 7.5
pH 1.2

FIGURE 3

FIGURE 4

Various actives coated with simple Ethylcellulose membranes. Release in pH 6.8 buffer in flow through cells.

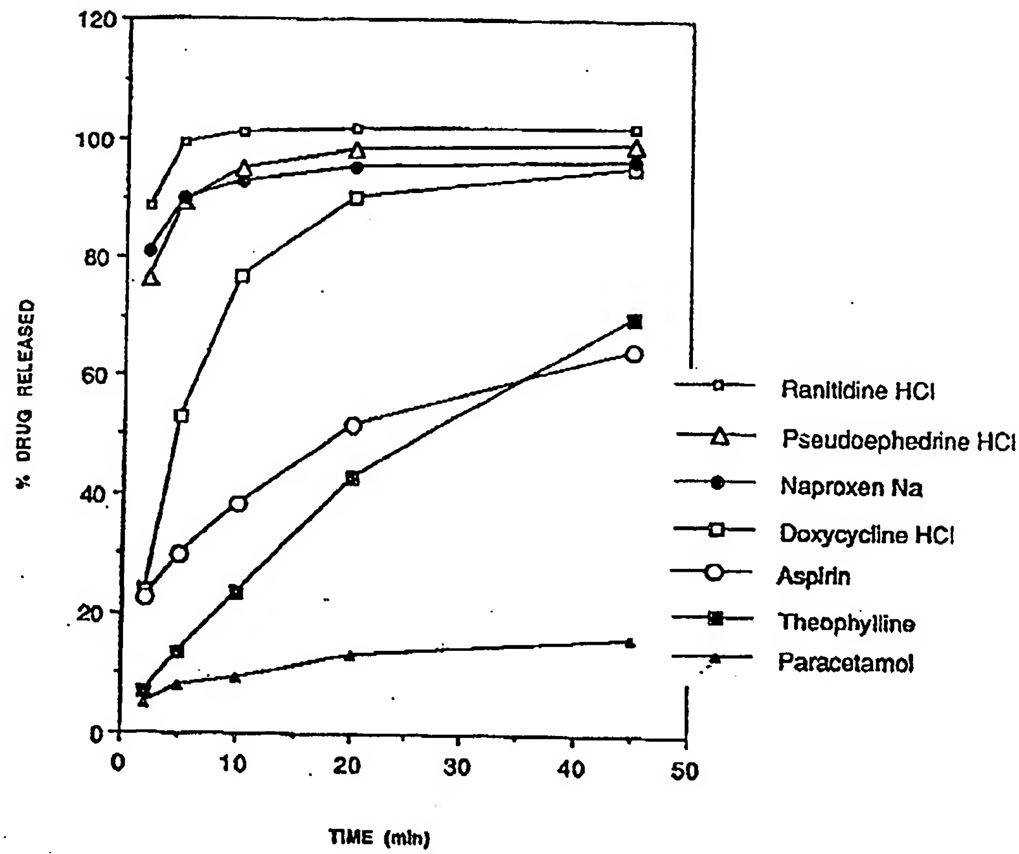

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FIGURE 5(A)

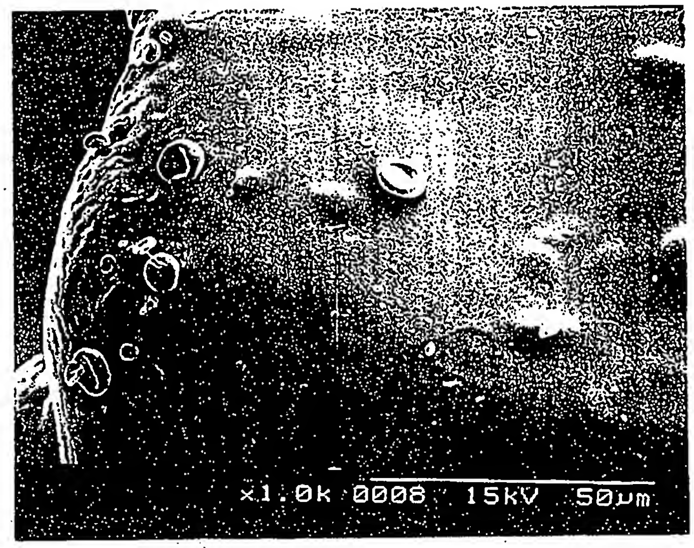
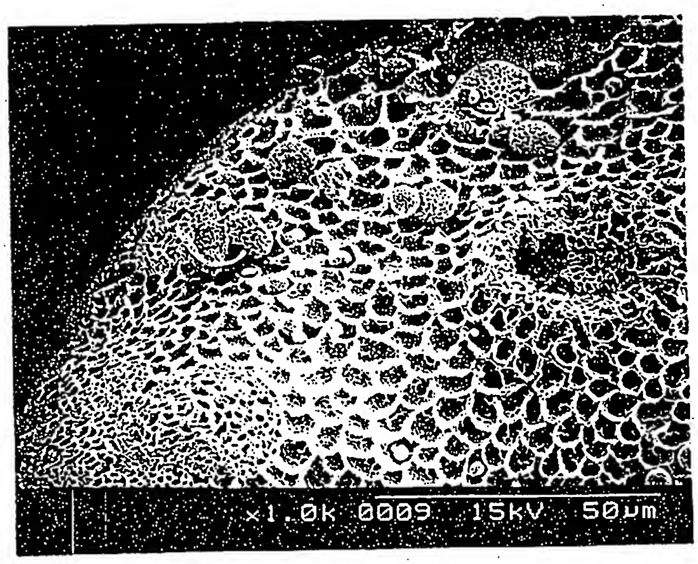


FIGURE 5(B)



Sim & McBurney

FIGURE 6

Comparison of release rates from ethyl cellulose coated paracetamol produced under conditions of dry and ambient inlet air.

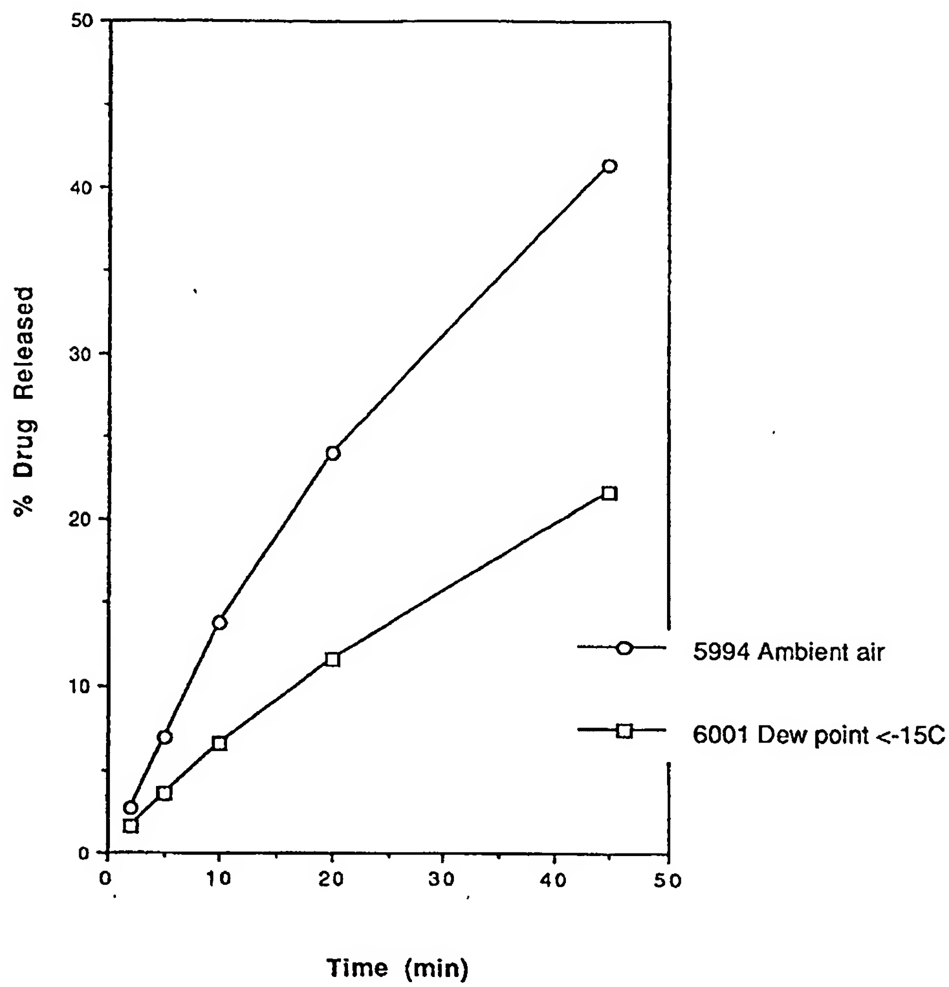


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FIGURE 7(A)

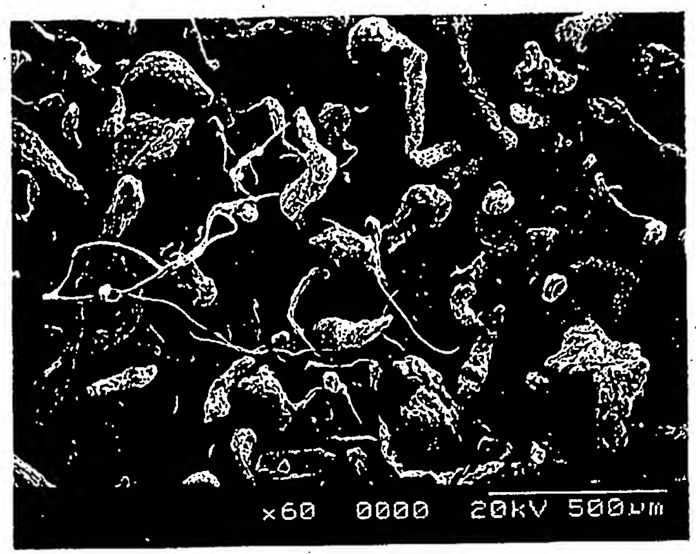

FIGURE 7(B)

Smart & Biggar

Percent Ranitidine HCl released from micro capsules comprising;
a) polymer membrane only,
b) wax sealed polymer membrane, and
c) a polymer coated wax membrane.

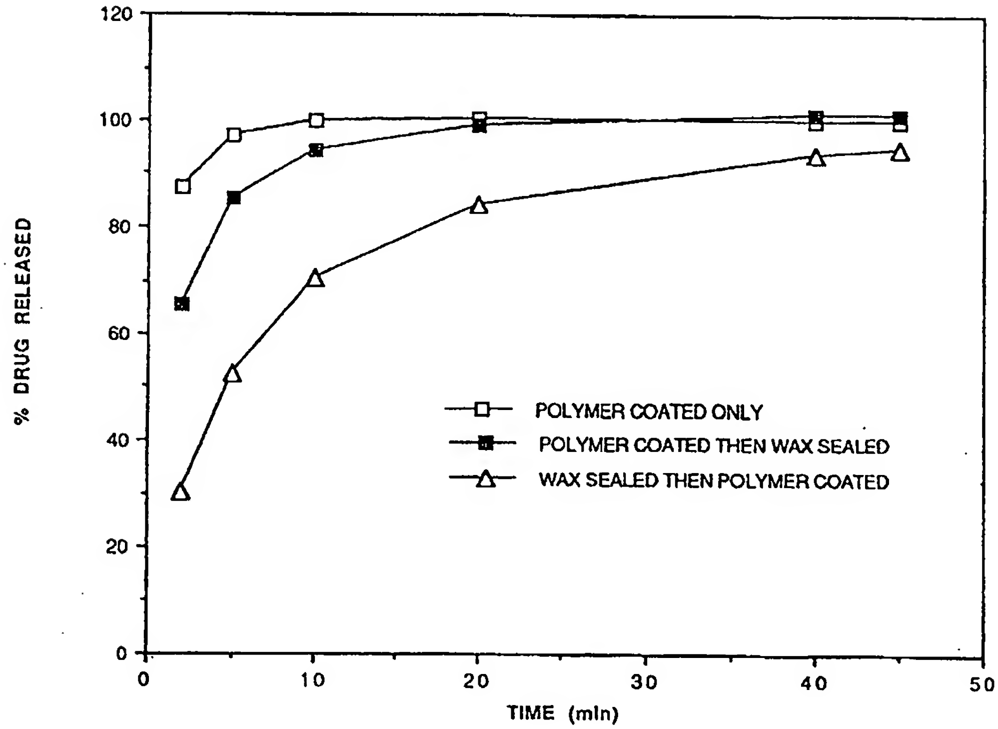

FIGURE 8